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REVIEW ARTICLE

Use of Aromatase Inhibitors in Postmenopausal Women With Advanced Breast Cancer

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Surgeons have been involved in the management of metastatic breast cancer since the technique of ovarian ablation was introduced in 1896. However, as newer hormonal and chemotherapeutic regimens were developed, drug therapy gradually replaced surgery as the preferred treatment for metastatic breast cancer. Thus, management of metastatic breast cancer has largely shifted from surgeons to medical oncologists. Advances in hormonal pharmacology have placed hormonal therapy alongside surgery and radiation therapy as a standard treatment option for women with advanced breast cancer. The purpose of this article is to update surgeons on the current use of hormonal agents for treatment of advanced breast cancer in postmenopausal women, and to review the aromatase inhibitors, a new line of hormonal agents for the treatment of advanced breast cancer.

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HORMONES FOR TREATMENT OF ADVANCED BREAST CANCER

One of the most challenging areas in breast cancer is the management of patients with metastatic disease. Even the most potent chemotherapy regimens produce only a modest reduction in tumor burden, and complete responses are invariably followed by relapse within 2–5 years. Therefore, the goals of treatment in advanced breast cancer are usually defined as palliation and the prevention of disease progression. Stated another way, the focus of intervention in patients with metastatic disease is improvement of the quality of life and extension of survival. The choice between hormonal manipulations and cytotoxic agents is individualized to the specific patient and her wishes. For example, while systemic chemotherapy is often indicated for symptomatic young patients with advanced disease at presentation, it is rarely indicated in the estrogen receptor-positive elderly patient with no symptoms or low volume of metastases.

Historically, hormonal manipulations included surgical ablative techniques such as oophorectomy [1], hypophysectomy, and adrenalectomy. Empiric hormonal therapies such as estrogens, androgens, corticosteroids, and progestins were also used, although the specific pharmacologic effects of these drugs were never well understood [2,3]. The response to either surgical or hormonal manipulations was poor, with 30% of patients re-

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sponding. Furthermore, this response was relatively short-lived as most patients relapsed within 1 year [4].

One important advance in the treatment of breast cancer was refinement of the assay procedures for estrogen and progesterone receptors. Many studies have shown that the presence of these receptors correlates with responsiveness to hormonal therapy in women with breast cancer [5,6]. Those patients with tumors positive for both estrogen and progesterone receptors have an average response rate to hormonal therapy of 70%, compared with response rates of 33% in patients with tumors positive for one receptor and 11% in patients with tumors negative for both receptors [7]. Further refinements of assay procedures have replaced the original dextran-coated charcoal assay with more precise biochemical methods to measure estrogen and progesterone receptor status. Endocrine manipulations for breast cancer treatment are now primarily directed at reducing the synthesis of estrogen or blocking estrogen receptors in those tumors that are hormone dependent.

FIRST-LINE TREATMENT FOR METASTATIC BREAST CANCER

Tamoxifen is currently the most widely used antiestrogen for the treatment of metastatic breast cancer and has been considered to be standard first-line treatment for advanced breast cancer in postmenopausal women since the late 1970s, when studies showed that it was as effective as other therapies used at that time but had fewer side effects [8,9]. While tamoxifen's pharmacologic action was originally described as competitive inhibition by blocking estrogen's binding to its receptor, recent studies have revealed additional actions of tamoxifen that may be of greater importance [10]. Tamoxifen has been found to have modulatory effects on immune function, and to simultaneously decrease levels of stimulatory growth factors (transforming growth factor-α and insulin-like growth factors) and increase levels of the inhibitory growth factor transforming growth factor β [11,12], which appears to inhibit the growth of estrogen receptor-negative tumor cells [13]. Other benefits from tamoxifen use included beneficial effects on bone mineral density [14] and a reduction in serum cholesterol levels [15], with a concomitant benefit on cardiovascular health [16,17].

Side effects associated with tamoxifen therapy include hot flashes, nausea, vomiting, vaginal bleeding, vaginal discharge, and menstrual irregularities. These symptoms are troublesome but usually tolerable. Other side effects associated with tamoxifen have raised some concern about its usage. Tamoxifen has been associated with thromboembolic disorders, as is seen with all hormonal therapies such as postmenopausal hormone replacement therapy and birth control pills. Large studies indicate that the combined incidence of cardiovascular events and pulmonary emboli is approximately 1.5% with fatal events occurring in less than 1% of tamoxifen users [16]. The risk of thromboembolic disorders is not generally considered to be significant when treating women with metastatic breast cancer.

Although tamoxifen has been shown to cause liver tumors in rats [18], no study to date has found a corresponding increased risk of hepatocellular cancer in humans in over 20 years of human use. A recent report has suggested a possible increase in stomach and colorectal cancer in patients receiving tamoxifen [19]; however, this finding has not been confirmed by other studies.

Perhaps the biggest area of concern is the reported two- to fivefold increased risk of endometrial cancer associated with long-term tamoxifen use that has been documented in both experimental and clinical studies [20,21]. In addition to adenocarcinoma, adenomyosis, and endometrial polyps, simple and adenomatous hyperplasia [22] have also been reported to be associated with prolonged use of this agent. Certainly, such risks need to be weighed against benefits of therapy, especially in women with metastatic disease.

SECOND-LINE AGENTS FOR TREATING METASTATIC BREAST CANCER

While second-line therapy traditionally consisted of endocrine organ ablation, procedures such as hypophysectomy and adrenalectomy have largely been abandoned because of the availability of effective pharmacologic hormonal preparations, e.g., progestins, aminoglutethimide, and luteinizing hormone-releasing hormone (LH-RH) agonists, which, like the surgical procedures, act to block secondary estrogen synthesis.

The progestins medroxyprogesterone acetate or megestrol acetate have been the most commonly used second-line endocrine agents for the treatment of advanced breast cancer in postmenopausal women. Approximately 25–35% of unselected women will typically respond to progestins [7]. In several randomized trials, these agents used as first-line treatments produced results similar to those produced by tamoxifen [11,23]. The mechanism of action of progestins in metastatic breast cancer is not well understood, although they probably reduce serum estrogens through feedback effects on the hypothalamic-pituitary-adrenal axis.

Progestins are associated with a high incidence of side effects, including nausea and vomiting, weight gain, hot flashes, vaginal bleeding, edema, hypercalcemia, rash, heart failure, hypertension, thrombocytopenia, depression, Cushingnoid symptoms, and occasionally, cardiovascular and thromboembolic side effects [24]. Therefore, while progestins are an effective second-line treatment for advanced breast cancer in postmenopausal

women, these adverse reactions have prompted the search for other second-line hormonal agents.

AROMATASE INHIBITORS

In postmenopausal women, ovarian steroid production declines with age. After menopause, estrogens are mainly produced in peripheral tissues such as adipose tissue and the adrenals [25]. This peripheral production is carried out by estrogen synthetase, or aromatase. Aromatase is an enzyme complex consisting of a cytochrome P-450 hemoprotein and a flavoprotein, and mediates the conversion of androstenedione and testosterone to estrone and estradiol, respectively, via a series of hydroxylation reactions.

In addition to aromatase activity in peripheral tissues, approximately two-thirds of breast tumors show aromatase activity, which apparently provides a local source of estrogens within the breast tumor [25]. Because estrogen production occurs outside of as well as within the endocrine glands, complete estrogen blockade is more likely to be accomplished by using systemic agents, like aromatase inhibitors, that can essentially shut off estrogen production, rather than surgically removing the endocrine glands.

There are two types of aromatase inhibitors: competitive and noncompetitive. Competitive inhibitors can be either steroidal or nonsteroidal compounds, while noncompetitive inhibitors are all steroidal. Both types of inhibitors mimic and compete with normal substrates for binding on the enzyme. The competitive inhibitors reversibly bind to the active enzyme site, while the noncompetitive inhibitors form an unbreakable covalent bond with the enzyme protein leaving the enzyme permanently inactivated.

The first generation of aromatase inhibitors were nonsteroidal competitive inhibitors of aromatase derived from glutethimide, including aminoglutethimide and pyridoglutethimide. Aminoglutethimide was the first aromatase inhibitor to be evaluated in clinical trials and has been available in Europe and Canada for over 20 years. Aminoglutethimide inhibits peripheral synthesis of estrogens, but has the pronounced side effect of blocking adrenal synthesis of both glucocorticoids and mineralocorticoids, thus requiring concurrent administration of hydrocortisone with its use. The second generation of aromatase inhibitors consisted of steroidal inhibitors such as lentaron and exemestane, and nonsteroidal competitive inhibitors such as fadrozole.

The third generation and newest aromatase inhibitors are nonsteroidal competitive inhibitors and are analogues of triazole. This class of drugs includes letrozole, vorozole, and anastrozole. These newest aromatase inhibitors have well-defined mechanisms of action and greater specificity and potency than earlier agents. Third-generation aromatase inhibitors do not inhibit adrenal steroid synthesis or affect other endocrine parameters, and thus corticosteroids are not required with their use [25]. Anastrozole, the only selective aromatase inhibitor currently approved for the treamtent of advanced breast cancer in postmenopausal women in the United States, does not cause excessive weight gain as does megestrol acetate. Anastrozole also has a low toxicity profile and convenient dosage schedule. More data are awaited on letrozole and vorozole.

The newest aromatase inhibitors offer advantages over other forms of endocrine therapy used in the management of patients with hormone-dependent breast cancer. The specific mechanism by which the new aromatase inhibitors block both peripheral and intratumoral estrogen production is well defined, whereas the current use of pharmacologic doses of steroidal hormones such as progestins and androgens is based on empirical evidence alone. The biologic activity of aromatase inhibitors can be precisely measured, thus allowing for direct comparisons of potency and specificity.

Table I summarizes the aromatase inhibitors currently in clinical use or being investigated in research studies [26].

CLINICAL STUDIES

Anastrozole

The advantages of anastrozole over earlier agents are increased selectivity and fewer side effects. Results of recent phase I and II studies demonstrated the efficacy and safety of anastrozole [27]. A 1-mg daily dose given to postmenopausal women suppressed serum estradiol to levels barely detectable by standard assays. Recently, anastrozole and megestrol acetate were compared in two prospective randomized phase III studies of postmenopausal women whose disease had progressed on tamoxifen therapy [28–31].

The two studies were conducted simultaneously in North America (383 patients) and in Europe (378 women). Postmenopausal women with advanced breast cancer were randomly assigned to receive 1 mg or 10 mg of anastrozole daily or 40 mg of megestrol acetate four times a day. The studies included patients with measurable disease and patients with evaluable disease, and objective tumor responses were based on International Union Against Cancer response criteria. Specifically, complete response meant disappearance of all metastatic lesions, whereas partial response was a greater than 50% regression in the sum of all measurable lesions. In these studies, complete and partial responses were verified by successive tumor assessments made by a panel of observers, performed at least 4 weeks apart.

Specific end points included objective response, duration of response, and time to disease progression. In pa-

TABLE I. Clinical Properties of Promising Aromarase Inhibitors

Compound	Selectivity	Status
Formestane 4-hydroxy androstenedione-ene-3, 17-dione	+++	Commercially available outside U.S.
Exemestame 6-methyleneandrosta-1,4-diene-3,17-dione	++	Phase I
Rogletimide (+/−)-2-ethyl-2-(4-pyridyl) glutarimide	+	Phase II
Fadrozole (+/−)-p-(3,6,7, 6-tetrahydroimidazo (1,5-a) pyridin-5-yl) benzonitrile monohydrochloride	++	Phase III completed
Letrozole 4,4′-(1H-1,2,4-triazol-l-ylmethylene) bis-benzonitrile	+++	Phase III
Vorozole (+)-6-(4-chloro-alpha-(1,2,4-triazol-l-yl)benzyl)-l-methyl-1h-benzotriazole	+++	Phase III
Anastrozole 2,2′[5-1*H*-1,2,4-triazol-1-ylmethyl)-1,2-phenylene]bis(2-methylpropiononitrile)	+++	Available in U.S. as of 1996

tients with nonmeasurable disease, responses could be classified only as complete response, stable disease for more than 24 weeks, or progressive disease. Greater than 60% of patients in both studies had bone metastases, for which it is difficult to quantitate the response. Response data for both studies are summarized in Table II.

Response rates were similar in each treatment arm of both studies. The median time to disease progression was the same for patients receiving anastrozole (141 days) and for patients receiving megestrol acetate (139 days). Among patients treated with anastrozole, 34.1% had either an objective response (complete or partial response) or stable disease for more than 24 weeks. Follow-up data on this study have demonstrated a possible survival advantage of 1 mg anastrozole compared with megestrol acetate [Buzdar AU, unpublished data, 1997]. At a median follow-up of 31 months, the overall survival in the 1-mg anastrozole group was 26.7 months vs. 22.5 months in the megestrol acetate group ($P = 0.02$); the 2-year survival rates were 56.1% vs. 46.3%, respectively.

An equal proportion of patients (3–5%) in each of the three treatment groups discontinued treatment because of severe adverse events. The most common adverse events in the megestrol acetate group were weight gain, edema, dyspnea, and thromboembolic events. In the anastrozole group the most common side effects were hot flashes, nausea, and vaginal dryness. Significantly more megestrol acetate patients than anastrozole patients gained at least 5% or 10% of their body weight; 34.4% of patients in the megestrol group had ⩾5% weight gain, compared with 13% and 14% of patients in the 1-mg and 10-mg anastrozole groups, respectively, while 10.7% of megestrol acetate patients experienced ⩾10% weight gain compared with 2% and 3%, respectively, in the anastrozole group.

Fadrozole

Fadrozole hydrochloride is another nonsteroidal aromatase inhibitor. Based on a phase II study in which approximately 20% of postmenopausal women with metastatic breast cancer responded to fadrozole [31], this drug was evaluated in comparison to megestrol acetate in a prospective randomized fashion. A total of 683 patients who had received prior therapy with tamoxifen were assigned to treatment with either 1 mg of fadrozole twice daily or 40 mg of megestrol acetate four times per day in double-blinded fashion [31].

The data from these two studies are shown in Table III. The median times to disease progression in the first study were 116 days for fadrozole and 114 days for megestrol acetate. In the second trial the median times to progression were 158 days for fadrozole and 174 days for megestrol acetate. Fadrozole has also been compared directly to tamoxifen as first-line therapy for metastatic breast cancer, with no statistically significant different in response rates and time to treatment failure between these two agents [32] (Table IV).

Clinical Data Summary

These data indicate that anastrozole and fadrozole have therapeutic efficacy similar to that of megestrol acetate in the treatment of metastatic breast cancer, the currently used second-line agent, but with improved side effect profiles. These drugs may ultimately prove to be better second-line agents for the treatment of metastatic breast cancer in postmenopausal women.

CURRENT INDICATIONS FOR USE OF AROMATASE INHIBITORS

In those patients with metastatic breast cancer who are candidates for endocrine manipulations after having received a complete 5-year course of tamoxifen as adjuvant therapy, traditional choices have included megestrol acetate, medroxyprogesterone acetate, and androgens. The newer nonsteroidal aromatase inhibitors such as fadrozole and anastrozole may be found to be useful in this

TABLE II. Objective Responses in Prospective Studies of Anastrozole vs. Megestrol Acetate Following Tamoxifen Therapy

	Anastrozole 1 mg	Anastrozole 10 mg	Megestrol acetate
U.S. study [Refs. 27, 28]			
Number of Patients	125	130	128
CR	3.1%	0.8%	1.6%
PR	7.0%	4.6%	3.9%
SD >24 weeks	26.6%	23.8%	29.7%
CR+PR+SD	36.7%	29.2%	35.2%
European study [Refs. 29, 30]			
Number of Patients	135	118	125
CR	1.5%	2.5%	2.4%
PR	8.9%	10.2%	8.0%
SD >24 weeks	23.7%	21.2%	22.4%
CR+PR+SD	34.1%	33.9%	32.8%

CR = complete response; PR = partial response; SD>24 weeks = stable disease for more than 24 weeks.

TABLE III. Objective Responses in Two Prospective Studies of Fadrozole HCl vs. Megestrol Acetate

	Response rate	
	Fadrozole HCl	Megestrol acetate
First study	n = 196	n = 184
CR	2.1%	4.3%
PR	9.2%	12.0%
SD	24.6%	19.6%
PD	64.1%	64.1%
Second study	n = 152	n = 151
CR	2.7%	2.7%
PR	10.7%	8.8%
SD	24.0%	29.7%
PD	62.7%	58.8%

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

TABLE IV. Fadrozole HCl vs. Tamoxifen as First-Line Therapy for Metastatic Breast Cancer [32]*

Parameter	Fadrozole HCl	Tamoxifen	*P* values
	n = 86	n = 90	
CR	4 (16%)	6 (24%)	0.19
PR	10	16	
NC	48	48	
PD	24	20	
Median TTF (months)	4.9	8.3	0.1
Toxicities (includes crossover patients)	n = 113	n = 123	
Thromboembolic events	0	2	
Hot flashes	18	26	
Nausea + vomiting	6	5	
Skin	3	0	
Other	7	16	

CR = complete response; PR = partial response; NC = no change; PD = progressive disease; TTF = time to failure.

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situation, given their similar efficacy and improved side effect profile compared to the progestins.

There are limitations to the use of aromatase inhibitors in breast cancer. Patients with estrogen receptor-negative tumors and patients who did not respond to previous tamoxifen therapy rarely respond to any of the aromatase inhibitors. There still remains a need for effective therapeutic regimens for this group of patients.

POTENTIAL FUTURE USES OF AROMATASE INHIBITORS

There are several potential uses for aromatase inhibitors in addition to their use as second-line agents as described above. For example, their role in premenopausal breast cancer patients remains to be elucidated. These agents may also be utilized in the treatment of male breast cancer. Since the safety profile of these drugs is favorable, there is a need to evaluate aromatase inhibitors as initial endocrine therapy of metastatic breast cancer.

While tamoxifen is the preferred first-line endocrine therapy of choice in patients with estrogen receptor-positive metastatic breast cancer, an aromatase inhibitor might be considered as an alternative first-line therapy in patients with significant history of thromboembolic disease or other contraindications to tamoxifen use.

The potential use of aromatase inhibitors as adjuvant therapy for early stage breast cancer is currently being explored. There is also a scientific rationale for using aromatase inhibitors in chemoprevention trials, as in various animal model systems inhibitors of estrogen synthesis have been effective in preventing breast cancer [33].

The newer and more potent aromatase inhibitors are remarkable in their effective inhibition of both peripheral and intratumoral aromatase. This series as a theoretical basis for treatment of other tumors such as pancreatic carcinoma, endometrial cancer, and prostate cancer, which all appear to both synthesize and respond to estrogens [33].

SUMMARY

The major indications for the use of aromatase inhibitors as hormonal therapy for advanced breast cancer can be summarized as follows: 1) Hormonal therapy has been proven to be effective for the treatment of advanced breast cancer; with a response rate of approximately 30% in unselected patients; the response rate is greater in patients with tumors positive for estrogen and/or progesterone receptors. 2) Aromatase inhibitors have been shown to be an effective second-line treatment for advanced breast cancer in postmenopausal women after first-line treatment with tamoxifen. The only FDA-approved selective inhibitor, anastrozole, has a more tolerable side effects profile than other second-line agents, such as megestrol acetate, and may possibly prolong sur-

vival. 3) Selective aromatase inhibitors are a useful new hormonal therapy for second-line treatment of advanced breast cancer and may prove to be useful for other indications such as first-line treamtent of advanced breast cancer and adjuvant treatment for early stage breast cancer.

This review has attempted to summarize the pharmacologic developments in hormonal therapy of breast cancer, and to introduce the selective inhibitors of the aromatase enzyme pathway as new players in this arena [34]. There is clearly a role for the newer, refined aromatase inhibitors alongside tamoxifen in the treatment of hormone-dependent breast cancers [35,36]. Although hormonal agents have largely supplanted surgery in the treatment of metastatic breast cancer, it is in our interest as surgeons to remain abreast of the developments in this field and to enthusiastically investigate these new pharmacological approaches.

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